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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/002,278	11/02/2001	Thomas M. Jessell	40314-A/JPW/MVM	3060

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	9

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/002,278	Applicant(s) JESSELL ET AL.	
	Examiner Eileen O'Hara	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,19,20,22-27 and 36-48* is/are pending in the application.

4a) Of the above claim(s) *17,20,22-27 and 36-40* is/are withdrawn from consideration.

5)☒ Claim(s) *19* is/are allowed.

6)☒ Claim(s) *41-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *17,19,20,22-27 and 36-48* ~~are~~ were subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 17, 19, 20, 22-27 and 36-48 are pending in the instant application.

Election/Restriction

2. Applicant's election with traverse of Group I in Paper No. 8, and the mouse polypeptide set forth in SEQ ID NO: 9, is acknowledged. The traversal is on the ground(s) that the claims of Group I are not independent of Groups II-VIII, and that they do not define patentably distinct inventions. Applicants note that 35 U.S.C. § 121 states, in part, that "[i]f two or more independent and distinct inventions are claimed in one application, the Commissioner may require the application to be restricted t one of the inventions." Applicants assert that under M.P.E.P. §802.1, "independent" means "there is no disclosed relationship between the subjects disclosed, that is, they are unconnected in design, operation and effect" , and the claims of Group I drawn to dorsalin-1 polypeptides are related to the claims of Groups II-VIII in that the claims in all groups are related to dorsalin-1 polypeptides and methods of using the dorsalin-1 polypeptides, and are therefore related. Applicants further assert that two or more independent and distinct inventions have not been claimed in the subject application because the groups are not independent under M.P.E.P. 802.1, and therefore the restriction is improper under U.S.C. § 121. Applicants additionally point out that under M.P.E.P. §803, the Examiner must examine the application on the merits, even though it includes claims to distinct inventions, if the search and examination of an application can be made without serious burden, and maintain that claims 17, 19, 20, 22-27 and 36-48 define a single inventive concept, and that a prior art search of the dorsalin-1 polypeptides will reveal whether any prior art exists as to uses of dorsalin-1 polypeptides.

This is not found persuasive because under the statute an application may properly be required to be restricted to one of two or more claimed inventions only if they are able to support separate patents and they are either independent (MPEP § 806.04- § 806.04(I)) **or** distinct (MPEP § 806.05-§ 806.05(I)).

Under MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 8702.01, 806.04, 808.01) **or** distinct as claimed (see MPEP § 806.05 - § 806.05(I): and

(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a) - § 806.04(I), § 808.01(a), and § 808.02).

The term "distinct" means that two or more subjects as disclosed are related, for example, as combination and part (subcombination) thereof, process and apparatus for its practice, process and product made, etc., but are capable of separate manufacture, use or sale as claimed, and are patentable (novel and unobvious) over each other (though they may each be unpatentable because of the prior art). It will be noted that in this definition the term related is used as an alternative for dependent in referring to subjects other than independent subjects. (MPEP § 802.01). Where inventions are related as disclosed but are distinct as claimed, restriction may be proper (MPEP § 806(B)). Even though the dorsalin-1 polypeptides are related to the method of using them, they are distinct inventions.

Consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable

together: (C) a different field of search:. These criteria were met in the above restriction. Therefore, the restriction is maintained.

The requirement is still deemed proper and is therefore made FINAL.

Claims 17, 20, 22-27 and 36-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. XX.

Claims 19 and 41-48 are currently under examination.

Priority

3. This application filed under former 37 CFR 1.60 lacks the current status of the nonprovisional parent application 08/065,844. A statement reading "(now United States Patent No. 6,333,168)" should be included after "08/065,844 filed May 20, 1993" following the title on the first sentence of the specification.

Drawings

4. Figure 1 of the instant application is presented on two separate panels. 37 C.F.R. § 1.84(U)(1) states that when partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by the same number followed by a capital letter. The two sheets of drawings which are labeled " Figure 1" and "Figure 1 Continued" in the instant specification should be renumbered "Figures 1A and 1B". Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84(U)(1), Applicant is required to file an amendment under 37 C.F.R. § 1.312 to change the Brief Description of the Drawings and the rest of the specification

accordingly. If, for example, Figure 1 is divided into Figures 1A and 1B, then the Brief Description and all references to this figure in the specification must refer to Figures 1A and 1B.

Claim Objections

5. Claim 41 is objected to because of the following informalities: claim 41 is objected to because it encompasses a non-elected invention, which should be deleted.

Appropriate correction is required.

Specification

6. The disclosure is objected to because of the following informalities:

6.1 On page 15, lines 15-17, the legend to the figure describes the dashed line outlines in figures D and **G**, but the dashed line outlines are in figures D and **J**.

6.2 The address of the ATCC has been changed. The correct address is:

American Type Culture Collection

10801 University Boulevard

Manassas, VA 20110-2209

Correction is required on pages 20 and 23 of the specification.

6.3 The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "Dorsalin-1 Protein".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 41-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 41 encompasses a pharmaceutical composition comprising an isolated dorsalin-1 polypeptide, and claims 42-48 encompass pharmaceutical compositions comprising an amount of isolated dorsalin-1 polypeptide effective to stimulate neural crest cell differentiation, to regenerate a nerve cell in a subject, to promote bone growth in a subject, to promote wound healing in a subject, to inhibit neural tumor cell growth in a subject, wherein the neural tumor is a neurofibroma or a Schwann cell tumor. Thus the claims encompass a "pharmaceutical use" for the compositions. For the claims to be enabled, the specification must teach how to use the composition for at least one pharmaceutical use without undue experimentation. Steadman's Medical Dictionary (24th Edition, 1982) defines "drug" as "a therapeutic agent; any substance other than food, used in the prevention, diagnosis, alleviation, treatment or cure of disease in man and animal." Ansel et al. (Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Edition), says "A drug is defined as an agent intended for use in the diagnosis, mitigation, treatment, cure or prevention of disease in humans or in other animals. One of the most astounding qualities of drugs is the diversity of their actions and effects on the body." The

following are examples of "pharmaceutical uses": administering vitamin supplements (preventing disease); using labeled antibodies for in vivo imaging (diagnosing disease); administering a substance to alleviate a symptom of a disease (alleviating or treating disease); and administering an antibiotic (curing bacterial infection). Administering a polypeptide to produce antibodies to protect the individual from contracting a disease, i.e., vaccination, is a pharmaceutical use, however, administering a polypeptide to produce antibodies which are then collected from the animal and used in various ways is not a pharmaceutical use.

In the present situation, to enable a pharmaceutical use for the dorsalin-1 polypeptide requires the specification to teach how to use the substance, without undue experimentation, for the prevention, diagnosis, alleviation, treatment or cure of a disease in the animal to which the substance is administered. However, the specification does not provide adequate guidance as to how the dorsalin-1 polypeptides can be used to treat or diagnose any disorders. The specification on pages 4-6 and 24-26 asserts that the dorsalin-1 proteins will have uses including stimulating neural crest cell differentiation, regenerating nerve cells, promoting bone growth, promoting wound healing, inhibiting neural tumor cell growth, wherein the neural tumor is a neurofibroma or a Schwann cell tumor.

However, there are no examples of treatment by administration of dorsalin-1. There are a number of *in vitro* experiments in chick embryos that demonstrate that dorsalin-1 is selectively expressed by cells in the dorsal region of the neural tube, and its expression in ventral regions appears to be inhibited by signals from the notochord and Henson's node (Figures 4 and 5 and page 38, line 29 to page 41, line 19). Figure 6 and page 41, line 21 to page 44, line 33, demonstrates that dorsalin-1 induces migration of cells from neural plate explants. Figures 7-8

and page 44, line 35 to page 47, line 1, demonstrate that the induction of Islet-1+ cells (Islet-1 is a marker for induction of motor neurons) in [i]-neural plate explants by contact with notochord or floor plate can be inhibited by dorsalin-1. On page 53, lines 12-19, the specification states:

> "In the neural tube, the dorsal restriction of dsl-1 mRNA by early signals from the notochord could generate a gradient of dsl-1 activity along the dorsoventral axis of the neural tube. Alone, or in conjunction with ventralizing signals from the notochord and floor plate, a gradient of dsl-1 could influence the fate of cells according to their dorsoventral position within the neural tube."

All of the examples in the instant application are directed to determining the functions and activities of the polypeptide in developmental chick embryo systems. There are no working examples of treatment of an animal for any disorder. It is not predictable from the *in vitro* experiments of the instant specification or from the teachings of the prior art that the dorsalin-1 polypeptides could be used to treat the diseases or disorders asserted in the specification.

Due to the lack of direction or guidance in the specification, the absence of working examples and teachings of the prior art, the unpredictability in the art, and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use a "pharmaceutical composition" comprising dorsalin-1 polypeptides. However, the specification enables the use of "a composition" comprising the dorsalin-1 polypeptides and a pharmaceutically acceptable carrier. Deletion of the word "pharmaceutical" before the word "composition" in claims 41 and 42 would obviate the rejection for these claims, since the specification has demonstrated that dorsalin-1 does stimulate neural crest cell differentiation which can be used in an *in vitro* system. However, compositions comprising a dorsalin-1 polypeptide effective for regenerating nerve cells, promoting bone growth or wound healing, or

inhibiting tumor cell growth in a subject are not enabled, since the specification has not provided support for these activities in a subject.

Pertinent Art

8. The art considered pertinent to the present application is Wozney et al., US Patent No. 5,661,007 (cited by Applicants), which discloses a polypeptide identified as bone morphogenic protein-9 (see SEQ ID NO: 9), which is 97.7% identical to the polypeptide of SEQ ID NO: 9 of the present application (see attached sequence alignment). This is not considered prior art, since the protein of Wozney et al. is different from that of dorsalin-1 of the instant invention. This reference does not teach or suggest what is being claimed, but is cited as the protein having the closest homology.

Conclusion

9.1 Claim 19 is allowed.

9.2 Claims 41-48 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Patent Examiner